

A schematic age-structured compartment model of the impact of antiretroviral therapy on HIV incidence and prevalence

⁽¹⁾School of Medicine of the University of São Paulo
and LIM01/HCFMUSP,

Av. Dr. Arnaldo, 455, CEP 01246-903, SP, Brazil

⁽²⁾Department of Infectious and Tropical Diseases (Hon. Prof.),
London School of Hygiene and Tropical Medicine,
London, UK

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Abstract

A simple deterministic model is proposed to represent the basic aspects concerning the effects of different antiretroviral treatment schedules on HIV incidence and prevalence of affected populations. The model mimics current treatment guidelines applied in Brazil. However, the model does not intend to fit the data with any acceptable degree of accuracy since uncertainties on the values of the parameters and on the precise effect of the treatment put some limits on the practical implications of our model from which only orders of magnitude and some qualitative effects can be deduced. So, this paper intends to provide a conceptual and mechanistic understanding of the possible long term effects of treatment on the dynamics of HIV transmission.

According to the model, the effect of the treatment depends on the level of sexual activity of the subpopulations considered, being more pronounced on the subpopulations with the highest sexual activity.

levels. Also, inefficient treatment can be prejudicial depending on the level of sexual activity and on the capacity to provide adequate treatment coverages to the population affected.

1 Introduction

The natural history of the Human Immunodeficiency Virus (HIV) infection and transmission is well understood today. It is now accepted that the viral concentration in the circulating blood (viraemia) and other organic fluids determines the probability of transmission [1]. It has been demonstrated by several authors that after infection the viraemia rapidly increases in the first week to a high level, staying in that high levels for some weeks, dropping afterwards to very low levels and then increasing slowly for several years. After a period of 10 - 15 years, the increasing level of viraemia reaches a level in which clinical manifestations begin, coinciding with the dropping in the CD4 lymphocytes (the target cell of HIV) counting and the development of the conditions that define the state of full-blown AIDS.

So, it should be expected a large variation in the probability of transmission of HIV along the natural course of the infection [2]. The relative contribution of each of these distinct phases of viraemia seen along the natural history of the infection to HIV transmission have only recently been demonstrated [3]. This relative contribution may have important consequences to the epidemiological pattern of HIV transmission, as well as to the assessment of the impact of HIV treatment on the epidemiology of HIV/AIDS. In addition, it should be expected that differences in the probability of transmission in each of the distinct phases of the infection may also have important consequences on the evolution of HIV virulence [4].

The use of the combined antiretrovirus therapies (ARVTs), particularly those known as HAART (highly active antiretrovirus therapies) has demonstrated excellent results in all the countries where people infected by HIV has access to the treatment [5]. The results reported significant reduction in deaths rates caused by opportunistic infections. For example, in the U.S.A. there has been a reduction of 61% between 1995 and 1997 in the mortality due to AIDS. In Brazil, whose experience has been acclaimed worldwide as one of the most successful attempts to control AIDS, the government decided to provide ARVT to all HIV seropositive individuals who fulfilled the treatment criteria. From 1996 onwards HAART has been used as a standard

treatment, with 120,000 patients being treated in 2002.

The treatment against HIV evolved rather rapidly. Just 4 years after the identification of HIV as the causative agent of the new syndrome, AIDS, zidovudine (AZT) the first drug for its treatment was licenced by the FDA. In the next eight years three other nucleoside analogs (the same class as zidovudine) were introduced. Concurrently, a better understanding of the dynamics of HIV replication and drug resistance mechanisms caused a shift from single- to combination-drug therapy. From 1995 to 1998 eight new antiretroviral agents were approved, including protease inhibitors and non-nucleosides transcriptase inhibitors . These latter drugs also provided clinicians with a highly effective antiretroviral therapy, known as HAART that reduces viral load by a factor of 10^3 . However, these new drugs cause several important side effects that limit their use. Because of this, current clinical guidelines propose a delaying in starting HIV treatment to a point in which either the viral load is high (above 30000 copies per ml) or the CD4 cell count is low. However, with the progression of the infection, even in the persistence of treatment, HIV viral load tends to increase again leading to a need to change the drugs in use or to progression to AIDS [6].

The discussion on the implications of antiretroviral antiretroviral treatment has been restricted to clinical and virological aspects. However, considering that different antiretroviral treatment strategies have distinct effects on viral load, one crucial aspect to be considered is the epidemiological consequences of a given antiretroviral treatment strategy on the incidence of new HIV infections. On one hand, effective antiretroviral treatment reduces viral load. On the other hand, it prolongs the asymptomatic phase, probably the most important for transmission [3] in the absence of antiretroviral treatment. Both effects are intrinsically related to transmission, although in opposite directions. Therefore, the critical question related to the choice of the best antiretroviral strategy should take into account the epidemiological consequences of different antiretroviral treatments. In spite of some attempts to understand this crucial aspect, the best antiretroviral treatment strategy is still to be defined [7],[8], [9].

In this paper we propose a schematic mathematical model to analyze the impact of current antiretroviral therapy on the incidence and prevalence of HIV infection. In section 2, we point out some historical aspects of Brazilian public health strategies related to HIV/AIDS treatment and its impact on the epidemics in Brazil. Our model was constructed incorporating the treatment concepts of the Brazilian program. However, due to uncertainties in param-

eters, practical conclusions should be taken with caution. In section 3, we derive an integral equation which allows the calculation of the impact on HIV incidence of an antiretroviral treatment program. This equation depends on a number of functions and parameters whose forms and values are described in section 4. In section 5, we present numerical results of several hypothetical scenarios and in section 6 we discuss the model's limitations and draw some tentative conclusions regarding possible epidemiological implications of our results.

2 Motivation: the Brazilian experience with HAART

Since 1991 the Brazilian government decided to provide ARVT to all HIV seropositive individuals who fulfilled the treatment criteria [10]. From 1996 onwards HAART has been used as a standard treatment, with 120,000 patients being treated in 2002. Its impact was immediately noted by health authorities, in particular its dramatic reduction on AIDS mortality, and this public health experience has been acclaimed worldwide as one of the most successful attempts to control AIDS.

Figure 1 shows the reduction in the mortality by AIDS in the period between 1996 and 2001. The total number of averted deaths summed up to 90,000 patients in this period.

Figure 1

In addition, it was observed an increase in the survival period of patients with AIDS, from 5 to 58 months, a 12 fold increase, after the introduction of HAART treatment. Also, there was a six-fold reduction in the number of AIDS hospitalizations and a reduction of 54% in the cost of treatment.

With respect to the impact of HAART on the incidence and prevalence of HIV infection, only rough estimates are available. For instance, in 1992 the World Bank projected the number of expected HIV infected individuals in Brazil by 2002 as 1.2 million. However, the current estimates for 2002 is around 600 thousands. It is difficult to attribute this reduction solely to HAART, since other preventive practices have been highly stimulated by the Brazilian government. For instance, the observed reduction in HIV infection prevalence among sex workers from 18% in 1996 to 6.1% in 2000, and

among homosexuals from 10.8% in 1999 to 4.7% in 2001, has been attributed by health authorities to the association of condom distribution and other preventive measures adopted.

The most important indication of the possible impact of HAART on HIV transmission in Brazil is the marked reduction in incidence rates of AIDS, as shown in figure 2. It is noticeable that after a historical increase in the incidences from 8 cases per 100,000 people per year in 1991 up to the peak of 18 cases per 100,000 people per year attained in 1998, the number of new cases dropped to 5 cases per 100,000 people per year in 2003. If we consider that the universal treatment started in 1996, we may conclude that after a delay of two years, the effect of HAART on the incidence of AIDS could be observed.

Figure 2

Notwithstanding, the observed reduction in HIV incidence and prevalence cannot be entirely explained by the effects due to HAART. Additionally, behavioral changes attributable to the preventive campaigns carried out in Brazil simultaneously to the beginning of HAART may also have had a positive impact on HIV transmission. For instance, there have been a marked increase in regular condom use verified between 1999 and 2000 (42% to 64%).

The Brazilian experience motivated us to model the possible role of ARVT on the incidence and prevalence of HIV. However, lack of data and uncertainties on the precise effect of the treatment put some limits on the practical implications of our model from which only orders of magnitude and some qualitative effects can be deduced.

3 The model: formalism

3.1 Sexually transmitted HIV

As in previous papers, we consider a community of N individuals in steady state with respect to time [3], divided into classes according to the contact pattern and transmission intensity of HIV [11]. For simplicity, in this paper we consider that the interaction between individuals from different classes is so rare that can be neglected. The classes will be described in section 5. As the interclass interactions are neglected, we describe a general formalism which applies to any and all classes.

Let $N(a)da$ be the number of individuals with age between a and $a + da$. Among those, let $X(a)da$ be the number of susceptibles with age between a and $a + da$. The number of unprotected sexual contacts per unit time those individuals with age between a and $a + da$ make with all other individuals with ages between a' and $a' + da'$ is:

$$\beta_0(a, a')da'X(a)da \quad (1)$$

Let $Y_1(a', \tau)da'd\tau$ be the number of individuals with age between a' and $a' + da'$ infected when aged between τ and $\tau + d\tau$. The number of unprotected sexual contacts per unit time those individuals with age between a and $a + da$ make with all other individuals with ages between a' and $a' + da'$ is

$$\beta_0(a, a')da'\frac{Y_1(a', \tau)da'd\tau}{N(a')da'}X(a)da \quad (2)$$

Let $g(a' - \tau)$ be the probability of a susceptible individual to get infected when making an unprotected sexual contact with an individual $Y_1(a', \tau)da'd\tau$. This depends on viral load which in turn depends on the time since infection ($a' - \tau$), and its form is given by equation (33). Therefore, the number of new infections per unit time, due to individuals $Y_1(a', \tau)da'd\tau$, is given by

$$\beta_0(a, a')g(a' - \tau)\frac{Y_1(a', \tau)}{N(a')}da'd\tau X(a)da \quad (3)$$

Let $Y_2(a', \tau, l)da'd\tau dl$ be the number of individuals with age between a' and $a' + da'$ infected when aged between τ and $\tau + d\tau$ and treated continuously after l , that is, the treatment is initiated between l and $l + dl$. Therefore, the fraction of the unprotected sexual contacts given by equation (1), with individuals with age a' and $a' + da'$ infected when aged between τ and $\tau + d\tau$ and treated between l and $l + dl$ is

$$\beta_0(a, a')da'\frac{Y_2(a', \tau, l)da'd\tau dl}{N(a')da'}X(a)da \quad (4)$$

Note that we assumed that the sexual behavior of susceptible towards treated and untreated infected individuals is the same.

Let $g_1(a' - l, l - \tau)$ be the probability of a susceptible individual to get infected when making an unprotected sexual contact with a treated individual $Y_2(a', \tau, l)da'd\tau dl$. This depends on viral load which in turn depends on the

time since infection ($a' - \tau$) and the time since the start of the treatment, and its form is given by equation (38). Therefore, the number of new infections per unit time, due to treated individuals $Y_2(a', \tau, l)da'd\tau dl$, is given by

$$\beta_0(a, a')g_1(a' - l, l - \tau)\frac{Y_2(a', \tau, l)}{N(a')}da'd\tau dlX(a)da \quad (5)$$

After integrating equation (3) from 0 to a' with respect to τ , and from 0 to infinite with respect to a' , and integrating (5) from τ to a' with respect to l , from 0 to a' with respect to τ , and from 0 to infinity, with respect to a' , and summing the two contributions, we get the so-called *per capita force of infection*, $\lambda(a)$, defined as

$$\begin{aligned} \lambda(a) = & \int_0^\infty \int_0^{a'} \beta_0(a, a')g(a' - \tau)\frac{Y_1(a', \tau)}{N(a')}d\tau da' \\ & + \int_0^\infty \int_0^{a'} \int_\tau^{a'} \beta_0(a, a')g_1(a' - l, l - \tau)\frac{Y_2(a', \tau, l)}{N(a')}dl d\tau da' \end{aligned} \quad (6)$$

As we showed in a previous paper [12], the contact function $\beta_0(a, a')$ must satisfy a symmetry relation. To see this, let

$$\beta_0(a, a')da'N(a)da \quad (7)$$

be the number of unprotected sexual contacts individuals with age between a and $a + da$ make with all individuals aged between a' and $a' + da'$. This number should be equal to the number of unprotected sexual contacts that individuals aged between a' and $a' + da'$ make with all individuals with age between a and $a + da$,

$$\beta_0(a', a)daN(a')da' \quad (8)$$

that is,

$$\frac{\beta_0(a, a')}{N(a')} = \frac{\beta_0(a', a)}{N(a)} \quad (9)$$

This can be satisfied if $\beta_0(a, a')$ is of the form

$$\beta_0(a, a') = f(a, a')\frac{N(a')}{N} \quad (10)$$

where $N = \int_0^\infty N(a)da$ is the total population and $f(a, a')$ is a symmetric function of a and a' , describing the per capita rate of unprotected sexual

contacts(see equations 29 and 30). Note that, due to the division by population size an increase in the frequency of age groups entirely uninterested for a given person will decrease his/hers sexual activity with those specific age groups. However, this is reflected automatically in the form of $f(a, a')$.

Substituting (10) in (6) we get

$$\begin{aligned}\lambda(a) = & \frac{1}{N} \int_0^\infty \int_0^{a'} f(a, a') g(a' - \tau) Y_1(a', \tau) d\tau da' \\ & + \frac{1}{N} \int_0^\infty \int_0^{a'} \int_\tau^{a'} f(a, a') g_1(a' - l, l - \tau) \\ & Y_2(a', \tau, l) dl d\tau da'\end{aligned}\quad (11)$$

Now, the equation for $X(a)$ is

$$\frac{dX(a)}{da} = -\lambda(a)X(a) - \mu X(a) \quad (12)$$

where μ is the natural mortality rate of humans.

Equation (12) can be integrated, resulting in

$$X(a) = X(0) \exp \left[- \int_0^a \lambda(s) ds - \mu a \right] . \quad (13)$$

Let us define $h_1(a, \tau)$ as a function describing the removal of individuals from the first infective condition by natural mortality and additional mortality due to progression to AIDS (see equation 35), and $h_2(a, \tau)$ describing the removal by antiretroviral treatment (see equation 37). Then we can write:

$$Y_1(a, \tau) = Y_1(\tau, \tau) h_1(a, \tau) h_2(a, \tau) \quad (14)$$

Now we have:

$$Y_1(a, a) = \lambda(a)X(a) \quad (15)$$

Substituting equation (13) in (15), we have:

$$Y_1(a, a) = X(0)\lambda(a) \exp \left[- \int_0^a \lambda(s) ds - \mu a \right] \quad (16)$$

Substituting (16) in (14) we get

$$\begin{aligned}Y_1(a, \tau) = & X(0)\lambda(\tau) \exp \left[- \int_0^\tau \lambda(s) ds - \mu \tau \right] \\ & h_1(a, \tau) h_2(a, \tau)\end{aligned}\quad (17)$$

Substituting equation (17) in (11) we get:

$$\begin{aligned}\lambda(a) = & \frac{X(0)}{N} \int_0^\infty \int_0^{a'} f(a, a') g(a' - \tau) \\ & \lambda(\tau) e^{-\int_0^\tau \lambda(s) ds - \mu\tau} h_1(a', \tau) h_2(a', \tau) d\tau da' \\ & + \frac{1}{N} \int_0^\infty \int_0^{a'} \int_\tau^{a'} f(a, a') \\ & g_1(a' - l, l - \tau) Y_2(a', \tau, l) dl d\tau da'\end{aligned}\quad (18)$$

Assuming a antiretroviral treatment rate $\nu(\tau, a)$, we have

$$Y_2(l, \tau, l) = Y_1(l, \tau) \nu(\tau, l) \quad (19)$$

and

$$Y_2(a, \tau, l) = Y_2(l, \tau, l) h_3(a, \tau, l) \quad (20)$$

where $h_3(a, \tau, l)$ is a function describing the removal of individuals from the treated condition by mortality (see equation 39 below). Then, substituting equations (17) in (19) and the resulting equation in equation (20), we get

$$\begin{aligned}Y_2(a, \tau, l) = & X(0) \lambda(\tau) \exp \left[- \int_0^\tau \lambda(s) ds - \mu\tau \right] \\ & h_1(l, \tau) h_2(l, \tau) h_3(a, \tau, l) \nu(\tau, l)\end{aligned}\quad (21)$$

so that we have

$$\begin{aligned}\lambda(a) = & \frac{X(0)}{N} \int_0^\infty \int_0^{a'} \lambda(\tau) e^{-\int_0^\tau \lambda(s) ds - \mu\tau} \\ & f(a, a') g(a' - \tau) h_1(a', \tau) h_2(a', \tau) d\tau da' \\ & + \frac{X(0)}{N} \int_0^\infty \int_0^{a'} \int_\tau^{a'} \nu(\tau, l) h_1(l, \tau) h_2(l, \tau) h_3(a', \tau, l) \\ & f(a, a') g_1(a' - l, l - \tau) dl d\tau da'\end{aligned}\quad (22)$$

Equation (22) always has $\lambda(a) = 0$ as a solution. Depending on the functions $f(a, a') g(a' - \tau)$, $f(a, a') g_1(a' - l, l - \tau)$ and on the parameters of $f(a, a') g(a' - \tau)$, $f(a, a') g_1(a' - l, l - \tau)$, $h_1(a', \tau)$, $h_2(a', \tau)$, $h_3(a', \tau, l)$ and $\nu(\tau, l)$, it may have another unique positive solution [3]. The condition for equation (22) to have another solution, that is $\lambda(a) \neq 0$ defines the threshold above which the infection can establish itself in the population [13], [14].

If we assume that $X(0)$ is proportional to the total population, $X(0) = bN$, where b is a constant, equation (22) becomes independent on the population size. In this paper we take $b = \mu$, for simplicity.

3.2 Parenterally transmitted HIV

In this subsection we model the parenteral transmission of HIV due to sharing contaminated syringes and needles or contaminated blood and blood products.

We consider that sexual transmission among these individuals is negligible when compared with the parenterally form of transmission. However, their contribution to the sexual spread of the infection will be considered in this section.

Let $Y_1^I(a', \tau)da'd\tau$ be the number of individuals parenterally infected with HIV (PI), aged between a' and $a' + da'$, who acquired the infection when aged between τ and $\tau + d\tau$. We consider that PIs enter this group when aged a_1 . We also consider that they form a proportion η of the population. Calling ξ the rate of sharing syringes (or receiving blood or blood products) multiplied by the probability of getting the infection if the syringe (or blood or blood products) is (are) infected, we have:

$$Y_1^I(a', \tau) = X(0)\eta\xi \exp[-\mu\tau] \exp[-\xi(\tau - a_1)] \theta(\tau - a_1) h_1(a', \tau) h_2(a', \tau) \quad (23)$$

where $h_1(a', \tau)$ and $h_2(a', \tau)$ were defined in the previous section and are the rates of removal from the infective class by death and treatment, respectively. Note that we have assumed that in the case of drug users, they remain drug users for the rest of their lives and that their mortality rate is not affected by the drug addiction. This simplification is partially supported by field work we carried out in the past [15], when we demonstrated that the average time of drug usage of the studied community was found to be around 10 years.

Assuming an antiretroviral treatment rate $\nu(\tau, a)$, we have

$$Y_2^I(l, \tau, l) = Y_1^I(l, \tau) \nu(\tau, l) \quad (24)$$

and

$$Y_2^I(a, \tau, l) = Y_2^I(l, \tau, l) h_3(a, \tau, l)$$

where $h_3(a, \tau, l)$ is a function describing the removal of individuals from the treated condition by mortality. Then, we get

$$Y_2^I(a, \tau, l) = h_1(a', \tau) h_2(a', \tau) h_3(a, \tau, l) \nu(\tau, l) \quad (25)$$

Dividing equations (23) and (25) by N , and adding to the corresponding terms in equation (11), we finally get, instead of (17) and (21):

$$\begin{aligned} Y_1(a, \tau) &= X(0)(1-\eta)\lambda(\tau) \exp\left[-\int_0^\tau \lambda(s)ds - \mu\tau\right] \\ &\quad h_1(a, \tau)h_2(a, \tau) + \eta X(0)\xi \exp[-\mu\tau] \\ &\quad \exp[-\xi(\tau - a_1)]\theta(\tau - a_1)h_1(a, \tau)h_2(a, \tau) \end{aligned} \quad (26)$$

and

$$\begin{aligned} Y_2(a, \tau, l) &= X(0)(1-\eta)\lambda(\tau) \exp\left[-\int_0^\tau \lambda(s)ds - \mu\tau\right] \\ &\quad h_1(l, \tau)h_2(l, \tau)h_3(a, \tau, l)\nu(\tau, l) \\ &\quad + \eta X(0)\xi \exp[-\mu\tau] \exp[-\xi(\tau - a_1)] \\ &\quad \theta(\tau - a_1)h_1(l, \tau)h_2(l, \tau)h_3(a, \tau, l)\nu(\tau, l) \end{aligned} \quad (27)$$

Finally, instead of (22) we get

$$\begin{aligned} \lambda(a) &= \frac{X(0)}{N} \int_0^\infty \int_0^{a'} (1-\eta)\lambda(\tau) \\ &\quad \exp\left[-\int_0^\tau \lambda(s)ds - \mu\tau\right] f(a, a')g(a' - \tau)h_1(a', \tau) \\ &\quad h_2(a', \tau)d\tau da' + \frac{X(0)}{N} \int_0^\infty \int_0^{a'} \eta \exp[-\mu\tau] \\ &\quad \exp[-\xi(\tau - a_1)]\theta(\tau - a_1)f(a, a')g(a' - \tau) \\ &\quad h_1(a', \tau)h_2(a', \tau)d\tau da' + \frac{X(0)}{N} \int_0^\infty \int_0^{a'} (1-\eta) \\ &\quad \lambda(\tau) \exp\left[-\int_0^\tau \lambda(s)ds - \mu\tau\right] f(a, a')g(a' - \tau) \\ &\quad \int_\tau^{a'} \nu(\tau, l)h_1(l, \tau)h_2(l, \tau)h_3(a', \tau, l)f(a, a') \\ &\quad g_1(a' - l, l - \tau)dl d\tau da' + \frac{X(0)}{N} \int_0^\infty \int_0^{a'} \eta \\ &\quad \exp[-\mu\tau] \exp[-\xi(\tau - a_1)]\theta(\tau - a_1) \\ &\quad \int_\tau^{a'} \nu(\tau, l)h_1(l, \tau)h_2(l, \tau)h_3(a', \tau, l) \\ &\quad f(a, a')g_1(a' - l, l - \tau)dl d\tau da' \end{aligned} \quad (28)$$

As mentioned before, if we assume that $X(0)$ is proportional to the population, for instance, $X(0) = \mu N$, the equation (28) becomes independent of the population size.

4 A schematic model

In this section we propose forms for the different functions involved in equation (28).

Let us begin with an untreated population, for which $\nu(\tau, l) = 0$ and $h_2(a', \tau) = 1$ so that the second part of the integral equation (28) vanishes.

As in [3], let us define the rate $f(a, a')$, in a very schematic form:

$$f(a, a') = f_0(a, a')\theta(a - a_0)\theta(a' - a_0) \quad (29)$$

where $f_0(a, a')$ is the rate of unprotected sexual contacts and a_0 is the age at which individuals enter in the risk behavior group. The Heaviside functions $\theta(a - a_0)$ and $\theta(a' - a_0)$ mean that sexual activity begins after age a_0 .

For the function $f_0(a, a')$, which describes the age preferences in acquisition of new partners and the age decline in the sexual activity, we propose:

$$f_0(a, a') = Q\beta_3(a)\beta_3(a')\beta_4(a - a') \quad (30)$$

where

$$\beta_3(x) = \frac{1}{\sqrt{2\pi}\sigma_1}e^{-\frac{(x-M)^2}{\sigma_1^2}} \quad (31)$$

and

$$\beta_4(a - a') = \frac{1}{\sqrt{2\pi}\sigma_2}e^{-\frac{(a-a')^2}{\sigma_2^2}} \quad (32)$$

The parameter M is the age of maximum sexual activity and the constant Q is adjusted to give the assumed average number of unprotected sexual contacts per unit time. Those forms for the β -functions (31) and (32) were chosen for convenience only and, although not supported by social studies, they conform with the following facts: a) sexual activity increases with age up to a maximum, decreasing thereafter; b) age preferences of an individual are distributed around a maximum value which we assumed to occur at the same age of the individual. In order to facilitate the calculations we made both functions as symmetric around a central value and we assumed a minimum age a_0 , below which there is no sexual activity. In addition we assumed that people without treatment, people undergoing treatment, and even people with full blown AIDS have the same sexual behavior. This assumption is supported by preliminary data in our community of HIV patients (Bueno, personal communication).

Let $A^{NT}(a' - \tau)$ be the viraemia level of non-treated individuals which depends on the time interval since the infection. For $g(a' - \tau)$ we take the form

$$g(a' - \tau) = I(A^{NT}(a' - \tau)) \quad (33)$$

where $I(A^{NT})$ is a function representing the transmission of at least one infective viral inocula, given the viremic level A^{NT} . As in [3] we assume that

$$I(A^{NT}) = (c' + c'' \log A^{NT})\theta(\log A^{NT} - 3) \quad (34)$$

where $c' = -3.35 \times 10^{-3}$ and $c'' = 1.2 \times 10^{-3}$ are parameters obtained by fitting equation (34) to the data by Gray et al. [20] (an almost identical relationship between log of viral load and transmissibility was found by using data from Vella et al [17] and Garcia et al [18], and it is supported by the observations of Fideli et al.[19] and Quin et al. [16]). The Heaviside function $\theta(\log A^{NT} - 3)$ is such that if $\log A^{NT} \leq 3$ there is no transmission.

For the removal of infected individuals, we assumed that when $(a' - \tau) < L_c$, where L_c is a given critical moment when individuals reach a certain viraemia level and are defined as AIDS patients, dies with rate μ . When $(a' - \tau) > L_c$, individuals are subjected to an additional, disease specific, death rate, α . A simple form for this removal function is:

$$\begin{aligned} h_1(a', \tau) = & e^{-\mu(a' - \tau)}\theta(L_c - (a' - \tau)) \\ & + e^{-\mu(a' - \tau) - \alpha((a' - \tau) - L_c)}\theta((a' - \tau) - L_c) \end{aligned} \quad (35)$$

Let us now consider the treated population. The variables and parameters already defined for the untreated population remain the same. We must only define values for $h_2(a', \tau)$, $\nu(\tau, l)$, $g_1(a' - l, l - \tau)$ and $h_3(a', \tau, l)$, where l is the moment in the history of the infection at which individuals begin to be treated.

Let $A^T(a' - l, l - \tau)$ denote the viraemia level after antiretroviral treatment. We assumed that the viraemia level after antiretroviral treatment is reduced by a certain factor, $\Delta(l - \tau)$, increasing thereafter as

$$A^T(a' - l, l - \tau) = \frac{A^{NT}(l - \tau)\Psi(a' - l)}{\Delta(l - \tau)} \quad (36)$$

where $\Psi(a' - l)$ is a given function with $\Psi(0) = 1$. Note that with such functions, the log of the viraemia level just after the beginning of the antiretrovi-

ral treatment starts with $\log [A^{NT}(l - \tau)] - \log [\Delta(l - \tau)]$ and increases with $\log [\Psi(a' - l)]$ thereafter.

Figure 3a schematically illustrates the natural history of HIV infection in the absence of antiretroviral treatment. Figure 3b illustrates the effect of antiretroviral treatment on the viraemia level.

Figure 3a
Figure 3b

In Figure 3a the viraemia level reaches a maximum immediately after the moment τ of the infection and drops rapidly after some few weeks, probably due to the effect of the immune system. Viraemia then starts to raise, and simultaneously a decrease in the counting of CD₄ T-lymphocytes is observed, until a critical viral load level is reached (L_c), when the immune system breaks down and full blown AIDS develops. This period lasts for 10 - 15 years.

Figure 3b represents the assumed natural history of HIV infection in the presence of antiretroviral treatment, which begins at the age of infection between l and $l + dl$. The treatment starts at any moment after the viral load reaches 30,000 copies/ml [21](we are well aware, however, that in real life other clinical indicators of antiretroviral treatment, like CD₄ counting, are used to begin the antiretroviral treatment.). We assumed that the treatment causes a sharp decrease in the viral load, and that it loses its effect immediately so that the viral load starts to rise log-linearly again. This intends to model the appearance of resistant strains, which we assumed to have the same virulence as the original strain. Therefore, the assumption of log-linearity in the viral load curve is entirely hypothetical and was intended to mimic an immediate development of full resistance by HIV to the treatment , which is the worst epidemiological scenario. In this situation, we are assuming that replication of HIV is no longer constrained by treatment. Another assumption of our model is that it takes no account of the role of the immunity system on HIV replication. With the above assumptions, the viral load after treatment increases until a critical level is eventually reached (L'_c), when the immune system breaks down and full blown AIDS develops. Hence, the treatment makes the period without AIDS longer than 10 years.

We assumed also that the antiretroviral treatment schedule is given by $\nu(\tau, l) = \nu \times \theta((l - \tau) - a_t)$, and it begins, as mentioned above, when viraemia reaches 30,000 copies/ml, which occurs at the infection age $(l - \tau) = a_t$

($\simeq 6.7$ years). Thus

$$h_2(l, \tau) = e^{-\nu \times ((l-\tau)-a_t) \times \theta((l-\tau)-a_t)} . \quad (37)$$

Since we assume that the treatment affects only the viral load, we may define $g_1(a' - l, l - \tau)$ as:

$$g_1(a' - l, l - \tau) = I(A^T(a' - l, l - \tau)) \quad (38)$$

Finally, for $h_3(a, \tau, l)$ we may also assume a simple form, similar to $h_1(a' - \tau)$:

$$\begin{aligned} h_3(a', \tau, l) &= h_3(a', l) = e^{-\mu(a'-l)\theta(L'_c - (a' - l))} \\ &\quad + e^{-\mu(a'-l)-\delta((a'-l)-L'_c)\theta((a' - l) - L'_c)} \end{aligned} \quad (39)$$

where L'_c is the new critical moment when treated individuals reach a certain viraemia level and are defined again as AIDS patients. Those patients are subjected to a new differential mortality rate δ due to AIDS.

Within this framework we can obtain different particular models by choosing suitable functions A^{NT} , A^T and constants.

We adopted, for the non-treated patients, the following average values for A_i and L_i :

$$A^{NT}(a' - \tau) = \begin{cases} A_1(a' - \tau) &= 10^6 \\ &\text{for } 0 \leq (a' - \tau) < L_1 \\ A_2(a' - \tau) &= 10^{3+0.22(a'-\tau-L_1)} \\ &\text{for } L_1 \leq (a' - \tau) < L_c \\ A_3(a' - \tau) &= 10^6 \\ &\text{for } (a' - \tau) \geq L_c \end{cases} \quad (40)$$

where $L_1 = 6$ weeks and $L_c - L_1 = \frac{3}{0.22}$ years is the period of time it takes for the viraemia to reach 10^6 RNA copies per ml since the beginning of the second phase.

Let us now model the effectiveness of antiretroviral treatment by an instantaneous reduction on the viral load immediately after the introduction of the treatment. We consider several effectiveness levels of antiretroviral treatment, by varying the reduction of the viral load. When the reduction is by a factor greater than 10^2 , the antiretroviral treatment is known as HAART (Highly Active AntiRetroviral Treatment). If the reduction is lesser than 10^2 ,

the antiretroviral treatment is known as non-HAART. Again, for the sake of simplicity, we drop the superscript T from the viral load A and introduce a subscript $j = 4, 5$, describing the two possible phases of the natural history of the infection after treatment. Note that we assumed no treatment during the first phase.

$$A^T((a' - l), (l - \tau)) = \begin{cases} A_4((a' - l), (l - \tau)) & = 10^{3-K+0.22(l-\tau-L_1)+0.22(a'-l)} \\ & \text{for } 0 \leq (a' - l) < L'_c \\ A_5((a' - l), (l - \tau)) & = 10^6 \\ & \text{for } (a' - l) \geq L'_c \end{cases} \quad (41)$$

where $L'_c = \frac{3+K-0.22(l-\tau-L_1)}{0.22}$ years, so that $\Psi(a' - l) = 10^{0.22(a'-l)}$, similar to the non-treated patients, and $\Delta(l - \tau) = K \geq 2$ for HAART treatment and $\Delta(l - \tau) = K < 2$ for non-HAART treatment. In the numerical simulations several values of K will be considered. Note that L'_c is the period of time it takes for the viraemia of treated individuals to reach 10^6 RNA copies per ml since the beginning of antiretroviral treatment.

With the above models of viraemia, $g(a' - \tau)$ takes the form

$$g(a' - \tau) = \begin{cases} I(A_1((a' - \tau))) & \text{for } 0 \leq (a' - \tau) < L_1 \\ I(A_2((a' - \tau))) & \text{for } L_1 \leq (a' - \tau) < L_c \\ I(A_3((a' - \tau))) & \text{for } (a' - \tau) \geq L_c \end{cases}, \quad (42)$$

where $I(A_1)$ is a function defined by equation (34), representing the probability of transmission of at least one infective viral inocula. Correspondingly, $g_1(a' - l, \tau)$ takes the form

$$g_1(a' - l, l - \tau) = \begin{cases} I(A_4((a' - l), (l - \tau))) \\ \quad \text{for } 0 \leq (a' - l) < L'_c \\ I(A_5((a' - l), (l - \tau))) \\ \quad \text{for } (a' - l) \geq L'_c \end{cases} \quad (43)$$

Finally, for the parenterally transmitted branch of the infection we take $\eta = 0.01$, $\xi = 0.05$ per year and $a_1 = 15$ years [15], [22].

5 Numerical results

In order to analyze the model's performance against an HIV endemic situation we solved equation (28) numerically for several treatment schedules. For

this we divided the population into four classes. Each class obeys an equation like equation (28) and intends to mimic a specific risk group, namely, group I (GI), with very low level of sexual promiscuity (84% of the total population), group II (GII) with moderate levels of sexual promiscuity (10%), group III (GIII) with high levels of sexual promiscuity (5%), and group IV (GIV) with very high levels of sexual promiscuity (1%). This somewhat arbitrary division is based on the actual classes of risk recognizable in real populations. So GI could represent the *general population*, GII *promiscuous heterosexuals*, GIII *male homosexuals*, and GIV *commercial sex workers and their clients*. We also assume that in each class there is a fraction η of *PIs*, who got infected by contaminated syringes/needles or blood/blood products. With respect to sexual contacts, it should be stressed that we are only interested in unprotected sexual contacts with new partners. In the functions β_3 and β_4 , which describe the sexual behavior, we set, for all classes, $\sigma_1 = 10$ years, $\sigma_2 = 15$ years, $M = 25$ years. The mortality (and fertility) rate was taken $\mu = 1/70 \text{ years}^{-1}$. The initial age of sexual life a_0 was set to 15 years.

The parameter Q is related, in the absence of the infection, to the per capita number of unprotected sexual contacts. We can, then, calculate the per capita number of unprotected sexual contacts in the population, Φ , as

$$\begin{aligned}\Phi &= \frac{1}{N} \int_0^\infty \int_0^\infty \beta(a, a') N(a) da' da \\ &= \mu \int_0^\infty \int_0^\infty \frac{f_0(a, a')}{N} \theta(a - a_0) \theta(a' - a_0) N(a') e^{-\mu a} da' da\end{aligned}\quad (44)$$

using equation (29). Using equation (30) we get the relation between the per capita number of unprotected sexual contacts in the absence of infection, Φ , and Q :

$$\Phi = \mu^2 Q \int_{a_0}^\infty \int_{a_0}^\infty \beta_3(a) \beta_3(a') \beta_4(a - a') e^{-\mu a'} e^{-\mu a} da' da\quad (45)$$

The parameter Q was adjusted to give the estimated average number of unprotected sexual contacts per unit time, Φ . The results, compatible with the literature, for each class were $Q = 6 \times 10^6$ (GI), $Q = 1.38 \times 10^7$ (GII), $Q = 1.45 \times 10^7$ (GIII), $Q = 1.55 \times 10^7$ (GIV), as can be seen in table 1.

With respect to the PI arm of transmission, as mentioned above, we chose the parameters $a_1 = 15$ years, $\eta = 0.001$ and $\xi = 0.05/\text{year}$.

Now, in the presence of HIV infection, without any treatment, the incidence of sexually transmitted HIV (i) is defined as the number of new cases of HIV infection per year per person and was calculated as

$$i = \frac{(1 - \eta) [\int_0^\infty \lambda(a) X(a) da]}{N} \quad (46)$$

and the incidence of parenterally transmitted HIV (i^I) is also defined as the number of new cases of HIV infection per year per person and was calculated as

$$i^I = \eta \mu \xi \int_0^\infty \exp[-\mu a] \exp[-\xi(a - a_1)] \theta(a - a_1) da \quad (47)$$

With the adopted parameters $a_1 = 15$ years, $\eta = 0.001$ and $\xi = 0.05$ per year, we have $i^I = 9 \times 10^{-6}$ per person-year.

The prevalence of sexually transmitted HIV (p) in the absence of treatment is given by

$$p = \int_0^\infty \int_0^a y_1(a, \tau) d\tau da \quad (48)$$

where

$$y_1(a, \tau) = \frac{Y_1(a, \tau)}{N} \quad (49)$$

where $Y_1(a, \tau)$ is given by equation (26) and $\lambda(a)$ given by equation (28), with $\nu(\tau, l) = 0$ and $h_2(a', \tau) = 1$. The prevalence of parenterally transmitted HIV (p^I), without treatment, is given by

$$\begin{aligned} p^I &= \int_0^\infty \int_0^a \eta \mu \xi \exp[-\mu \tau] \\ &\quad \exp[-\xi(\tau - a_1)] \theta(\tau - a_1) h_1(a, \tau) d\tau da. \end{aligned} \quad (50)$$

With the adopted parameters $a_1 = 15$ years, $\eta = 0.001$ and $\xi = 0.05/year$, we have $p^I = 5.9 \times 10^{-4}$.

The results of the simulation for the per capita number of unprotected sexual contacts, the prevalence and the incidence of HIV infection at equilibrium are given in table 1:

Table 1: prevalence and incidence of HIV infection at equilibrium

class(%)	$\Phi(years^{-1})$	without PI		with PI	
		incidence	prevalence	incidence	prevalence
GI(84%)	6.60 [24]	0.00	0.00	8.51E-05	1.25E-03
GII(84%)	15.30 [25]	7.09E-04	1.08E-02	1.20E-03	1.89E-02
GIII(84%)	16.00 [26]	2.60E-03	4.50E-02	2.75E-03	4.77E-02
GIV(84%)	17.10 [27]	4.60E-03	9.00E-02	4.63E-03	9.17E-02
Average(84%)	13.20	2.47E-04	4.23E-03	3.75E-04	6.24E-03

The scenario presented in table 1 is not intended to fit real data but rather to present qualitatively the effects of treatment. It is interesting, however, that the prevalence results are compatible with regions with intermediate levels of HIV transmission. By intermediate levels of HIV transmission, we mean regions of the world with HIV/AIDS prevalences ranging from 0.5% to 1.2%[23]. Note that without the PI class there would be no disease in the general population and the infection would be restricted to the other three classes. However, as mentioned before, our model is too schematic to guarantee that the above conclusion can be extended to any real population.

Note also that in table 1 the ratio between i and Φ , which gives the number of new cases of HIV infection per unprotected sexual relation with each new partner. So, for instance, considering the class GIV, our results point to a risk of acquiring HIV infection of approximately 3.0% per unprotected sexual contact. This result is of the same order of that reported in the literature (for instance, in Thailand this risk was estimated to be between 3.1% and 5.6% [28]).

In order to evaluate the impact of antiretroviral treatment on the incidence and prevalence of HIV infection we simulated the model for values of K (effectiveness of treatment) ranging from 0 to 3 and ν (intensity of treatment) ranging from 0.05 to 0.5. The impact of antiretroviral treatment on the incidence and prevalence of HIV infection in each class is shown in figures 4 to 8. Figure 4 shows the effect of antiretroviral treatment on the class representing GI ($Q = 115,000$). In this class the risk of contracting HIV is very low, reaching a prevalence without antiretroviral treatment of the order of 0.1%. In fact, this low prevalence is due to the PI individuals, without whom the disease among the general population would disappear, meaning that for $Q = 115,000$ the infection is below the threshold for its maintenance in the general population. Figures 4a and 4b show the incidence and prevalence, respectively, as functions of the intensity of antiretroviral treatment ν for six levels of effectiveness of antiretroviral treatment K . Note that the infection drops monotonically with ν for all values of K .

Figure 4a
Figure 4b

Figure 5 shows the effect of antiretroviral treatment on the class representing the subpopulation GII ($Q = 138,000$). In this class the risk of contracting HIV is higher than in the GI, described above. Without antiretroviral treatment the prevalence of HIV infection reaches the order of

2.0%. Figures 5a and 5b show the incidence and prevalence, respectively, as functions of the intensity of antiretroviral treatment ν for six levels of effectiveness of antiretroviral treatment K . Note that for $K = 0.5$ the treatment results in higher prevalence and incidence than in its absence, for all values of ν . Moreover, both the incidence and the prevalence show an initial increase with the treatment intensity and a decrease after around $\nu = 0.15$.

Figure 5a
Figure 5b

To understand the phenomenon described above, one should consider the following: first, a low intensity treatment means that the individuals, on the average, start to be treated later than with a high intensity treatment; secondly, starting the treatment implies in reducing the probability of HIV transmission proportionally to the reduction in the log of viral load due to the effect of the treatment; finally, treating individuals implies in a longer survival period, therefore increasing the total number of sexual contacts of those individuals. Hence, if the effectiveness of the treatment (K) does not reduce the log of the viral load sufficiently to decrease the probability of transmission per sexual contact such as to compensate the increased transmission of HIV due to the higher number of sexual contacts, the total contribution of those individuals to HIV transmission will increase. Otherwise it will decrease. This effect repeats itself for the other simulations described below.

Figure 6 shows the effect of antiretroviral treatment on the class representing the subpopulation of GIII individuals ($Q = 145,000$). In this class the risk of contracting HIV is higher than that of GII, described above. Without antiretroviral treatment the prevalence of HIV infection reaches the order of 4.8%. Figures 6a and 6b show the incidence and prevalence, respectively, as functions of the intensity of antiretroviral treatment ν for six levels of effectiveness of antiretroviral treatment K . Note that, for $K = 0.5$ the prevalence and the incidence is greater than without treatment for all values of ν . For $K \geq 1$, the incidence drops monotonically with ν . However, for $K = 1$, the prevalence is greater than that without treatment for values of ν up to approximately 0.8.

Figure 6a
Figure 6b

Figure 7 shows the effect of antiretroviral treatment on the class representing the subpopulation GIV ($Q = 155,000$). In this class the risk of contracting HIV is the highest among all classes considered. Without antiretroviral treatment the prevalence of HIV infection reaches the order of 9%. Figures 7a and 7b show the incidence and prevalence, respectively, as functions of the intensity of antiretroviral treatment ν for six levels of effectiveness of antiretroviral treatment K . Note that both the incidence and the prevalence for $K = 0.5$ are higher than those without treatment, for all values of ν . For $K = 1$ and $K = 1.5$, the incidence drops monotonically but the prevalence is greater than that without treatment for small values of ν .

Figure 7a
Figure 7b

Figure 8 shows the weighted average of the incidence (8a) and prevalence (8b) curves over the entire population. Note that both the incidence and the prevalence for $K = 0.5$ are higher than those without treatment, for all values of ν . For $K \geq 1$, both the incidence and prevalence drop monotonically.

Figure 8a
Figure 8b

6 Comments and conclusions

In this paper we presented a very simple model of the steady-state effect of HAART on HIV incidence and prevalence. The model mimics current treatment guidelines applied in Brazil. However, the model does not intend to fit the data with any acceptable degree of accuracy since detailed information necessary are not available. So, this paper intends to provide a conceptual and mechanistic understanding of the possible long term effects of treatment on the dynamics of HIV transmission. As mentioned by Anderson [29], one of the purposes of modelling is to help identifying areas in which better epidemiological data is required to refine prediction and improve understanding, guiding, in a way, field research. We hope our model can be useful in pointing which parameters should be better determined in future studies.

The model could be extended to allow the calculation of temporal evolution of the effects of treatment on HIV incidence, as we did for rubella

vaccination in [12]. At the present stage we calculated only steady-state effects, which is important enough for assessing long term effects of treatment on trends of HIV dynamics.

One important aspect of the model is that the population was divided into four compartments according to their sexual activities. We also assumed another compartment of PIs and we assumed that only they interact with the other four different model compartments. The PIs were singled out because they acquire the infection by a different route. It would appear natural to consider that the risk groups would interact with each other. However, this would introduce more unknown parameters and, therefore, for simplicity we considered such an interaction as negligible. Note that this implies that if an individual from any single risk group, for instance GI, has an unprotected sexual contact with any other individuals from another group he/she and his/her stable partner would be considered as belonging to this class.

Our main conclusions are as follows:

1. The disease, according to the model, is almost completely wiped out when we consider the most effective treatment ($K = 3.0$) simulated. This conclusion should be taken with great care since it may be the result of some 'mathematical pathology' taken to its extreme. In fact, the model predicts that under this treatment regime the disease is maintained in the population (all four classes) due to the interaction of individuals from the other classes with PIs. Again, this conclusion should be taken with caution since, by allowing strong interactions between the distinct sexual behavior classes the disease might not disappear under treatment. In addition, note that our simulated treatment represents the worst scenario (the immediate evolution of complete resistance with no further alteration in the treatment scheme), while in clinical practice modifications of treatment schemes should always follows a significant increase in viraemia.
2. The impact of the treatment on HIV incidence or prevalence depends on the level of sexual activity of the subpopulations considered, being more pronounced on the subpopulations with the highest sexual activity levels. By impact of treatment we mean the difference between the pre-treatment level of incidence or prevalence and the equilibrium attained with the maximum intensity of treatment, ν . This conclusion is valid only for the most effective treatment scheme, $K = 3.0$

- Inefficient treatment, $K < 1.0$, can be prejudicial on the subpopulations with high levels of sexual activity. For instance, in populations with intermediate levels of sexual activity ($\Phi = 0.153 \text{ years}^{-1}$), the effect of inefficient treatment depends on the intensity of treatment, ν , in a curious way. For ν between 0 and 0.15, there is an increase in both incidence and prevalence, which then drops thereafter. The reason for this behavior is explained in the main body of the text.

As a general comment, there are many ways to express the intensity of transmission of an infection, among which the classical basic reproduction ratio, R_0 , the force of infection, $\lambda(a)$, the incidence and the prevalence. The basic reproduction ratio is the greatest eigenvalue of the Frechet derivative with respect to $\lambda(a)$ of the operator, which is the right hand side of equation 28, calculated at $\lambda(a) = 0$ (see [13], [30]). In this paper we calculated the incidence and the prevalence of HIV as these are the parameters most used by public health authorities to monitor HIV epidemic.

Finally, since HIV treatment begins late in the second phase (in practice and in this model), the intensity and diversity of effects that result from different treatment strategies is another evidence of the importance of the asymptomatic phase of HIV infection on the spread of the virus. This has already been pointed out [31], contrasting with former opinions of some infectious disease practitioners and epidemiologists.

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Captions for the figures

Figure 1: Reduction in the mortality by AIDS in the period between 1996 and 2001. The total number of averted deaths summed up to 90,000 patients in this period.

Figure 2: Reduction in the incidence rates in Brazil two years after the introduction of universal highly active antiretroviral treatment.

Figure 3: (a) Model assumed to describe the natural variation of HIV viraemia along the natural history of the infection (shaded area). The infection happens at age between τ and $\tau + d\tau$ and L_c marks the beginning of full blown AIDS. (b) Model assumed to describe the natural variation of HIV viraemia along the natural history of the infection in presence of antiretroviral treatment (shaded area). The infection happens at age between τ and $\tau + d\tau$, the treatment begins at age between l and $l + dl$ and L'_c marks the beginning of full blown AIDS.

Figure 4: (a) The incidence of HIV in the GI (general population) group as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K . (b) The prevalence of HIV in the GI (general population) group as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K .

Figure 5: (a) The incidence of HIV in the class representing the sub-population of GII (promiscuous heterosexuals) group, as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K . (b) The prevalence of HIV in the class representing the sub-population GII (promiscuous heterosexuals), as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K .

Figure 6: (a) The incidence of HIV in the class representing the sub-population GIII (male homosexuals), as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K . (b) The prevalence of HIV in the class representing the sub-population GIII (male homosexuals), as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K .

Figure 7: (a) The incidence of HIV in the class representing the sub-population GIV (sex workers) and their clients, as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K . (b) The prevalence of HIV in the class representing the sub-population GIV (sex workers) and their clients, as a function of the treatment intensity

rate ν for several levels of effectiveness of antiretroviral treatment K .

Figure 8:(a) The incidence of HIV in the population average as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K . (b) The prevalence of HIV in the population average as a function of the treatment intensity rate ν for several levels of effectiveness of antiretroviral treatment K .

Figure 1
AIDS mortality in Brazil

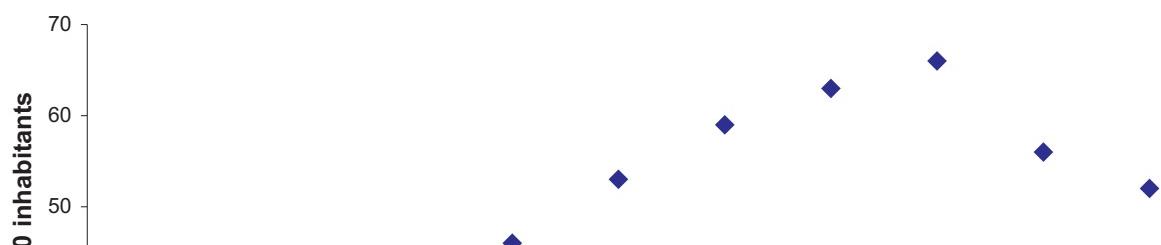


Figure 2
Incidence of AIDS in Brazil

